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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,251	06/06/2002	Keizo Inoue	04853.0089	7644

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EXAMINER

BERTOGLIO, VALARIE E

ART UNIT	PAPER NUMBER
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1632

12

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Office Action Summary</p>	Application No. 10/069,251	Applicant(s) INOUE ET AL.	
	Examiner Valarie Bertoglio	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-34 is/are rejected.
- 7) ☒ Claim(s) 34 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 June 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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Response to Amendment

Applicant's arguments filed 04/18/2003, paper number 11, have been fully. Claims 14-26 have been cancelled. Claims 27-34 have been added. Claims 27-34 are pending and under consideration in the instant action.

Claim Objections

Claim 34 is objected to because of the following informalities:

Claim 34 depends from rejected claim 33. Rewriting claim 34 in independent form would overcome this rejection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 29, 31 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous transgenic mouse whose genome comprises a knockout allele of the α -TTP gene wherein the mouse exhibits reduced fertility, does not reasonably provide enablement for a heterozygous transgenic mouse whose genome comprises a knockout allele of the α -TTP gene wherein the mouse exhibits reduced fertility or for chimeric mice comprising cells comprising a knockout allele of the α -TTP gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 27 encompasses both heterozygous and homozygous mice comprising a knockout allele of the α -TTP gene wherein the homozygous mice exhibit a vitamin E deficiency and the heterozygous mice

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have any phenotype. Claim 29 encompasses both heterozygous and homozygous mice comprising a knockout allele of the α -TTP gene wherein the mice exhibit a failure of pregnant females to maintain pregnancy as assayed by the fetal resorption test. Claim 33 encompasses methods of making a chimeric mouse comprising cells comprising a knockout allele of the α -TTP gene.

The specification fails to enable making and using a heterozygous mouse comprising a knockout allele of the α -TTP gene wherein the mouse has any phenotype. The claim fails to recite a phenotype for the heterozygous mouse and therefore encompasses any and all phenotypes. The art at the time of filing held that the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the γ_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Because the phenotype of transgenic knockout animals is unpredictable, one of skill in the art would not know how to make or to use the claimed animal wherein said animal displays any phenotype other than the phenotype of vitamin E deficiency as described in the specification. Furthermore, it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to make and use a heterozygous mouse comprising a knockout allele of the α -TTP gene wherein the mouse displays any phenotype other than vitamin E deficiency.

The specification fails to enable making a heterozygous mouse comprising a knockout allele of the α -TTP gene wherein the mice exhibit a failure of pregnant females to maintain pregnancy as assayed by the fetal resorption test (claim 29). It was well known in the art at the time of filing that vitamin E

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deficiency can lead to fetal resorption as evidenced by the vast usage of the fetal resorption test as a measure of vitamin E deficiency. The specification teaches that mice homozygous for a knockout allele of the α -TTP gene have undetectable levels of Vitamin E (page 20, lines 4-5) and this extreme deficiency leads to 100% failure to maintain pregnancy as assayed by the fetal resorption test (Table 2). The specification also teaches that mice heterozygous for a knockout allele of the α -TTP gene have reduced levels of Vitamin E (page 20, lines 5-6). The specification does not teach that the reduced levels of vitamin E in the heterozygous mice are reduced to a degree such that they result in absolute failure to maintain pregnancy. It would require undue experimentation for one of skill in the art to determine how to make a heterozygous mouse whose genome comprises a knockout allele of the α -TTP gene wherein the mouse exhibits a failure to maintain pregnancy as assayed by the fetal resorption test.

The specification fails to enable the method of producing a chimeric mouse comprising cells comprising a knockout allele of the α -TTP gene (Claim 33). The specification and the art at the time of filing enable making the chimeric mouse. However, one of skill in the art would not know how to use said mouse. The degree of chimerism in each chimera varies from animal to animal. There would be considerable variation from chimeric mouse to chimeric mouse in the levels of α -TTP produced and the level of vitamin E in various tissues of each mouse. Thus, the phenotype of the chimeric mice would be variable and unpredictable. One of skill in the art cannot predict the phenotype of the chimeric mice produced by the method of claim 33 and without knowing the phenotype of an mice, one of skill in the art would not know how to use the mice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 27-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is unclear because it encompasses both heterozygous and homozygous mice wherein only the homozygous mice have a phenotype. The specification supports that both heterozygous and homozygous mice exhibit a vitamin E deficiency, however, the claim only gives this limitation to the homozygous mouse and therefore encompasses heterozygous mice with any and all phenotypes.

Claims 27-32 are unclear because it is not known whether the claim intends to encompass chimeric mice as made by the method of dependent claim 33. It is well known in the art that a transgenic animal is one whose somatic and germ cells comprise a transgene and is not chimeric. An example of more clear claim language would be, "A transgenic mouse whose somatic cells and germ cells comprise a knockout allele of the genomic α -TTP gene..."

Claim 29, 31 and 33 are unclear because they refer to "The transgenic mouse according to claim 27", however, claim 27 encompasses two different mice, a heterozygous and a homozygous mouse. It is unclear to which mouse claim 29 is referring.

Claim 33 is unclear because it is a method of making a chimeric mouse; however, claim 33 depends from claim 27, which is drawn to a transgenic mouse that, by definition, is not chimeric.

Claim 34 is unclear because it is drawn to a method of producing a transgenic mouse, includes method step of mating mice (step a) by screening the progeny to identify a "non-human mammal" (step b). The term "non-human mammal" encompasses non-mouse species, however, mice cannot produce non-mouse species.

Conclusion

No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

PETER PARAS
PATENT EXAMINER



Valarie Bertoglio
Examiner
Art Unit 1632